

Psychological Medicine

Frontostriatal functional connectivity correlates with repetitive behaviour across autism spectrum disorder and obsessive-compulsive disorder --Manuscript Draft--

Manuscript Number:	PSM-D-17-01446R3
Full Title:	Frontostriatal functional connectivity correlates with repetitive behaviour across autism spectrum disorder and obsessive-compulsive disorder
Article Type:	Original Article
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Manuscript Region of Origin:	NETHERLANDS
Abstract:	<p>Background Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are neurodevelopmental disorders with considerable overlap in terms of their defining symptoms of compulsivity/repetitive behaviour. Little is known about the extent to which ASD and OCD have common versus distinct neural correlates of compulsivity. Previous research points to potentially common dysfunction in frontostriatal connectivity, but direct comparisons in one study are lacking. Here, we assessed frontostriatal resting state functional connectivity in youth with ASD or OCD, and healthy controls. In addition, we applied a cross-disorder approach to examine whether repetitive behaviour across ASD and OCD has common neural substrates.</p> <p>Methods A sample of 78 children and adolescents aged 8-16 years was used (ASD n=24; OCD n=25; healthy controls n=29), originating from the multicentre study COMPULS. We tested whether diagnostic group, repetitive behaviour (measured with the Repetitive Behavior Scale-Revised), or their interaction, was associated with resting state</p>

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Results

No diagnosis-specific differences were detected. The cross-disorder analysis, on the other hand, showed that increased functional connectivity between the left nucleus accumbens and a cluster in the right premotor cortex/middle frontal gyrus was related to more severe symptoms of repetitive behaviour.

Conclusions

We demonstrate the fruitfulness of applying a cross-disorder approach to investigate the neural underpinnings of compulsivity/repetitive behaviour, by revealing a shared alteration in functional connectivity in ASD and OCD. We argue that this alteration might reflect aberrant reward or motivational processing of the nucleus accumbens with excessive connectivity to the premotor cortex implementing learned action patterns.

Title: Frontostriatal functional connectivity correlates with repetitive behaviour across autism spectrum disorder and obsessive-compulsive disorder

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Wordcount: 4387

Funding: European Community's Seventh Framework Programme (FP7) - 278948

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Abstract

Background. Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are neurodevelopmental disorders with considerable overlap in terms of their defining symptoms of compulsivity/repetitive behaviour. Little is known about the extent to which ASD and OCD have common versus distinct neural correlates of compulsivity. Previous research points to potentially common dysfunction in frontostriatal connectivity, but direct comparisons in one study are lacking. Here, we assessed frontostriatal resting state functional connectivity in youth with ASD or OCD, and healthy controls. In addition, we applied a cross-disorder approach to examine whether repetitive behaviour across ASD and OCD has common neural substrates.

Methods. A sample of 78 children and adolescents aged 8-16 years was used (ASD $n=24$; OCD $n=25$; healthy controls $n=29$), originating from the multicentre study COMPULS. We tested whether diagnostic group, repetitive behaviour (measured with the Repetitive Behavior Scale-Revised), or their interaction, was associated with resting state functional connectivity of striatal seed regions.

Results. No diagnosis-specific differences were detected. The cross-disorder analysis, on the other hand, showed that increased functional connectivity between the left nucleus accumbens and a cluster in the right premotor cortex/middle frontal gyrus was related to more severe symptoms of repetitive behaviour.

Conclusions. We demonstrate the fruitfulness of applying a cross-disorder approach to investigate the neural underpinnings of compulsivity/repetitive behaviour, by revealing a shared alteration in functional connectivity in ASD and OCD. We argue that this alteration might reflect aberrant reward or motivational processing of the nucleus accumbens with excessive connectivity to the premotor cortex implementing learned action patterns.

Introduction

Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are neurodevelopmental disorders with a prevalence of about 1-3% in the general population (Ruscio *et al.* 2010; Lai *et al.* 2014) and are both characterized by the presence of compulsivity. Compulsivity can be defined as the performance of repetitive and functionally impairing overt or covert behaviour without adaptive function, performed in a habitual or stereotyped fashion (Fineberg *et al.* 2014). Parallels have been drawn between the restricted interests, repetitive sensory behaviours, and insistence on sameness seen in ASD, and the obsessions and compulsions seen in OCD (Jiujias *et al.* 2017). Moreover, even though DSM versions IV-TR and older did not allow for a comorbid diagnosis of ASD and OCD (American Psychiatric Association, 2000), a recent longitudinal registry study (Meier *et al.* 2015) and literature review (Jiujias *et al.* 2017) highlight the increased prevalence of OCD (symptoms) in ASD and vice versa. Between 17 and 37% of youth with ASD have been found to meet diagnostic criteria for OCD (Leyfer *et al.* 2006; van Steensel *et al.* 2011). Yet, little is known about the extent to which ASD and OCD have common versus distinct neural correlates of compulsivity. The identification of common correlates could point to overlapping neural mechanisms underlying compulsivity in these disorders and suggest that the compulsivity symptoms could be used as a cross-disorder stratification marker. This might facilitate the development of cross-disorder treatment strategies. Conversely, distinct neural correlates of compulsivity in ASD and OCD may ultimately be used as biomarkers to aid differential diagnosis, treatment selection, and outcome monitoring. So far, scarce direct comparisons of ASD and OCD revealed common functional alterations during reward/decision-making processes in frontostriatal regions such as the orbitofrontal cortex (OFC), nucleus accumbens (NAcc), anterior cingulate cortex (ACC), and caudate (Carlisi *et al.* 2017a, 2017b). In

addition, the current study (COMPULS) previously found heightened ACC glutamate concentrations in both ASD and OCD (Naaijen *et al.* 2017), further implicating frontostriatal circuitry. To expand upon this knowledge, we here examined this circuitry using a resting state functional connectivity approach.

Three partly segregated, parallel frontostriatal circuits are generally distinguished (Haber 2003; Langen *et al.* 2011; van den Heuvel *et al.* 2016). The limbic circuit consists of the NAcc, OFC, and other frontal regions and is involved in motivation and reward. The cognitive circuit includes the caudate nucleus and prefrontal areas and is responsible for more cognitive functions such as working memory. Lastly, the sensorimotor circuit between the putamen and sensorimotor cortical areas subserves motor learning and performance. These circuits run through the globus pallidus and thalamus and together promote flexible initiation and inhibition of behaviour. Dysfunction of these circuits is thought to underlie various forms of repetitive behaviour in psychiatric disorders such as OCD and ASD (Langen *et al.* 2011; van den Heuvel *et al.* 2016).

Classically, ASD and OCD have been studied as isolated disorders. Several studies have used resting state functional magnetic resonance imaging (R-fMRI), to examine striatal connectivity in either OCD or ASD. Findings for the specific diagnostic groups have been mixed in terms of direction (increased or decreased connectivity) and which specific frontal/cortical connections were affected. However, some patterns can be distinguished that are potentially shared between the disorders. Increased functional connectivity between the NAcc and OFC has been reported in both ASD (Delmonte *et al.* 2013; although see Padmanabhan *et al.* 2013) and OCD (Harrison *et al.* 2009, 2013; Sakai *et al.* 2011; Jung *et al.* 2013; Abe *et al.* 2015). Similarly, in both ASD and

OCD increased connectivity between caudate and ACC (ASD: Delmonte *et al.* 2013; OCD: Hou *et al.* 2013), as well as reduced connectivity of putamen with the middle and inferior frontal gyri (ASD: Padmanabhan *et al.* 2013; OCD: Bernstein *et al.* 2016; Harrison *et al.* 2009; Vaghi *et al.* 2017) have been observed.

In the abovementioned R-fMRI studies, ASD or OCD groups were assessed independently from one another. Yet, identification of the unique and shared patterns in frontostriatal connectivity between ASD and OCD requires investigation of both disorders in one study, without methodological differences hindering comparisons. Furthermore, previous studies adhering to the diagnostic categories ASD and OCD have yielded some conflicting results. This may be due to the diversity of symptoms within a disorder (Langen *et al.* 2011; Robbins *et al.* 2012), which could result in samples that have the same diagnostic label but have different clinical profiles. The sole reliance on diagnostic categories also creates artificial boundaries between disorders showing substantial overlap in symptoms, such as ASD and OCD, suggesting a distinction that may not be evident at the neurobiological level. Accordingly, investigation of the cross-disorder symptom domain of repetitive behaviour may reveal common neural substrates and thereby bring to light new possibilities for diagnostics and treatment (Langen *et al.* 2011).

In the present study, we aimed to elucidate both common and distinct alterations in resting state connectivity patterns of the striatum in ASD and OCD. To focus on childhood-onset OCD and avoid confound with late-onset OCD, which may have a different aetiology (Taylor 2011), we targeted the age range of 8-16 years. We first performed comparisons between both diagnostic groups and healthy controls. Second, we assessed the relation between striatal connectivity and

symptoms of repetitive behaviour across all groups, hereby transcending diagnostic classifications. Lastly, we explored the possibility of diagnosis by repetitive behaviour interactions, as repetitive behaviour symptoms may have different neural substrates in OCD compared to ASD. Based on the previous work described above, we hypothesized that repetitive behaviour across disorders would be associated with reduced connectivity between the putamen and inferior and middle frontal gyri, and increased connectivity of the NAcc and caudate with the OFC and ACC respectively.

Methods

Participants

The current sample consisting of ASD, OCD and healthy control participants originated from the COMPULS European multicentre study with four sites (see Naaijen *et al.* 2016 for the design paper of the study). Procedures were in accordance with the latest version of the Declaration of Helsinki and approved by regional ethics committees. Written informed consent was obtained from parents/guardians, oral assent from children < 12 years, and written assent from children aged 12 and older. Inclusion criteria for all participants were age 8-16 years, Caucasian decent, IQ>70, no major physical illness, no present or past neurological disorders (e.g. epilepsy) or head injuries, and no contraindications for MRI. Healthy controls and their first-degree family members had to be free of psychiatric disorders. Participants with ASD or OCD were not allowed to have a diagnosis of the other disorder of interest.

Data from two sites were excluded because of too few usable OCD datasets (<5). Inclusion in the statistical analyses would yield very small and unequal groups, leading to the inability to distinguish the effects of diagnosis from the effects of the added scanner sites. Remaining were 40 participants with complete R-fMRI data from King's College London, London, United Kingdom, and 88 participants from the Radboud University Medical Center and the Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands. Of these 128 participants, some were excluded based on MRI quality ($n=8$; discussed further in pre-processing section), incidental findings ($n=1$), or not meeting clinical criteria ($n=3$).

Healthy controls were over-recruited in Nijmegen. Therefore, a smaller control group from Nijmegen was matched to the OCD group from Nijmegen based on age, sex, and IQ using the full matching procedure of the package MatchIt (Ho *et al.* 2011) in R (R Core Team 2014). From London all available healthy control data was used. The final sample consisted of 24 children with ASD, 25 children with OCD and 29 healthy controls between the ages of 8 and 16 years. Numbers per site and detailed group characteristics are listed in Table 1.

Phenotypic Information

Before inclusion, healthy controls were screened with the Child Behavior Checklist and Teacher Report Form (Achenbach & Rescorla 2001), establishing that they had no subscale scores within the clinical range. Diagnosis of ASD (DSM-IV-TR criteria; American Psychiatric Association 2000) was confirmed by the structured autism diagnostic interview revised (ADI-R; Lord *et al.* 1994), assessing ASD symptoms throughout development. The severity of obsessions and compulsions in OCD was rated with the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill *et al.* 1997), in the form of an interview with both parent(s) and child present.

This interview was also applied to ASD or healthy control participants in case they had elevated OCD scores in the screening interview (see below). For all participants, repetitive behaviour was defined as the total score on the Repetitive Behavior Scale-Revised (RBS-R; Lam & Aman 2007), filled in by the parents. In order to screen for possible comorbidities such as attention-deficit/hyperactivity disorder (ADHD), parents of all participants were interviewed with either the structured Diagnostic Interview Schedule for Children (Shaffer *et al.* 2000) in London or the semi-structured Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman *et al.* 1997) in Nijmegen. In the event of an elevated score on one of the screening items, the full module for the respective disorder was administered. Parents further reported on past and present medication use. Full IQ was estimated by administration of four subtests of the Wechsler Intelligence Scale for Children-III (Wechsler 2002): block design, vocabulary, similarities, and picture completion.

Image acquisition

Participants were asked to refrain from using stimulant medication and caffeine from 48 hours before testing. On the testing day, they were first familiarized with the MRI context in a mock scanner. Resting state T2-weighted functional scans and reference T1-weighted anatomical scans were acquired on 3 Tesla MRI scanners (Nijmegen site: Siemens Prisma, Siemens, Erlangen, Germany; London site: General Electric MR750, GE Medical Systems, Milwaukee, WI, USA). Either a 32-channel (Nijmegen) or 8-channel (London) head coil was used. For the anatomical scan the sequence was based on the ADNI GO protocols (Jack *et al.* 2008) and for the R-fMRI we used a multi-echo sequence (Kundu *et al.* 2012). The scanning parameters are detailed in Supplementary Table 1 and were matched as closely as possible across the sites. During the R-

fMRI scan, the light was dimmed, a fixation cross was placed on the screen, and children were asked to keep their eyes open.

R-fMRI pre-processing

We employed a standard pre-processing pipeline incorporating functions from the FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl>). Echoes were combined using weighted averaging. To account for equilibration effects, the first five functional volumes were discarded. Head movement correction was performed by realigning functional images to the middle volume (MCFLIRT; Jenkinson *et al.* 2002). The pipeline further consisted of grand mean scaling, spatial smoothing using a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm, and ICA-AROMA. ICA-AROMA is an ICA-based tool to automatically identify and remove motion-related components from the data (Pruim *et al.* 2015a, 2015b). It includes a stringent classifier that relies on specific characteristics of signal related to head motion in order to identify noise components and subsequently regress them from the data. Although a specific method for denoising multi-echo data has also been gaining recognition (ME-ICA; Kundu *et al.* 2012), ICA-AROMA is among the top performing motion correction pipelines (Parkes *et al.* 2018) and has been shown to work equally well on multi-echo as on single-echo data (Pruim *et al.* 2015a). It is now widely applied to fMRI data of children and adolescents who are typically developing as well as those with clinical conditions (e.g. Chauvin *et al.* 2017; Yang *et al.* 2017). Finally, we applied nuisance regression to eliminate signal from cerebrospinal fluid and white matter, and high-pass filtering (0.01Hz). Resulting functional images were co-registered to the respective participant's anatomical scan using boundary-based registration in FSL-FLIRT (Greve & Fischl 2009). The anatomical scan was transformed into MNI152 standard space with 12-parameter affine

transformations, which was refined using non-linear registration with FSL-FNIRT (Andersson *et al.* 2010). By applying the warp fields of the previous steps, the concatenated R-fMRI data was also brought into standard space. Eight participants (ASD $n=2$; OCD $n=2$; Control $n=4$) were excluded based on poor quality and/or excessive head motion, i.e., participants belonging to the 5% with on average the highest mean root mean square of the frame-wise displacement across functional scans (RMS-FD >0.65 ; Jenkinson *et al.* 2002).

Seed definition

A seed-based approach was applied with seeds for the caudate nucleus, putamen and NAcc to investigate the different frontostriatal loops described in Langen *et al.* (2011). To define the seeds, we created subject-specific anatomical masks of these regions using the FSL-FIRST toolbox for automatic subcortical segmentation (Patenaude *et al.* 2011) and transformed these to MNI152-space. The FSL-FIRST output was visually inspected for evident segmentation errors. We took into account the functional distinctions between the anterior and posterior putamen (e.g. Helmich *et al.* 2010; von Rhein *et al.* 2016) by splitting the putamen at the reference point of the anterior commissure. We left a gap of 4 mm (2 voxels) between the anterior and posterior putamen to minimize signal overlap. Eight seed masks were used in total (NAcc, caudate, anterior putamen, posterior putamen; left and right analysed separately), see Supplementary Figure 1 for an example.

R-fMRI participant-level analyses

From the subcortical seed masks, we extracted the first eigenvariate of the timeseries of the R-fMRI activity in MNI152 standard space. Using the resulting timeseries, whole-brain voxel-wise connectivity with each seed was estimated in the context of the general linear model within FSL. Resulting connectivity maps were used for subsequent group-level analysis.

R-fMRI group-level analyses

First, ASD, OCD, and healthy control groups were compared using group-level analyses on the connectivity maps for each seed obtained in the previous step. To assess differences between the three groups, we applied permutation testing (5000 permutations) using FSL Randomise (Winkler *et al.* 2014), including covariates for age, sex, and scan-site. Voxel-wise testing was limited to the voxels within a frontal lobe mask, as defined with the MNI atlas (lowest probability threshold), which included the insular cortex.

Second, the association of repetitive behaviour with functional connectivity was investigated across all participants, including healthy controls. One participant was excluded from these analyses because of a missing RBS-R questionnaire. Both positive and negative associations between repetitive behaviour and voxel-wise functional connectivity of the respective seed regions were investigated using FSL Randomise with the same covariates as described above. In the event of a significant association, we computed partial correlations between extracted average connectivity estimates and the RBS-R total score, whilst controlling for age, sex, and scan-site. Depending on the distributions, either parametric Pearson's or non-parametric Spearman's correlations were used. Correlations were computed across the total sample in R. We also checked whether a correlation was present within patients, and within the ASD and OCD groups separately.

Lastly, in order to assess the possibility that repetitive behaviour symptoms have a different neural substrate in OCD compared to ASD, we conducted group \times repetitive behaviour interaction analyses within the two diagnostic groups, using a similar approach as above.

For each analysis, threshold-free cluster enhancement (TFCE) was used, as implemented in FSL (Smith & Nichols 2009). Significance was defined with a threshold of familywise error (FWE) corrected $p < 0.05$.

Sensitivity analyses

To investigate whether a significant cluster could alternatively be explained by IQ or head motion, we obtained partial correlations (Pearson or Spearman depending on the normality of the data) of the connectivity estimates with IQ and RMS-FD. In the event of a significant correlation, we reanalysed the significant cluster, whilst taking this confounding variable into account. To check the influence of outliers, we also reanalysed any significant effects after excluding outliers > 2.5 SD . The supplement details sensitivity analyses to ensure that age, scan-site, sex, medication use and comorbidity did not drive the significant results.

Results

Whole-brain functional connectivity of the striatal regions

As a check and illustration of the general connectivity patterns of the selected seeds (unrelated to clinical symptoms or diagnosis), Figure 1 depicts the whole-brain positive connectivity maps of the striatal seed regions in healthy controls. Only the maps for the left seeds are shown, but similar patterns were obtained for the right side. The NAcc was mainly connected with a cluster comprising ACC, medial prefrontal cortex (mPFC), and OFC, but connectivity with the caudate, hippocampal areas, and cerebellum was also present. The caudate displayed connectivity with

other striatal regions, ACC, OFC, mPFC, superior frontal gyrus, anterior insula, temporal regions and thalamus. The anterior and posterior putamen were connected to other striatal areas, thalamus, brainstem, cerebellum, insula, lateral prefrontal cortex, sensorimotor, temporal and posterior areas. Differences between the anterior and posterior putamen were evident in the ACC and mPFC, where the anterior putamen displayed more connectivity. The posterior putamen showed more extensive connectivity with sensorimotor, cerebellar and posterior areas. Note that differences between anterior and posterior putamen connectivity were not tested for statistical significance. Together, the observed connectivity patterns were roughly in line with established CSTC networks (Alexander *et al.* 1986; Di Martino *et al.* 2008; von Rhein *et al.* 2016).

Group-level analyses of striatal-frontal connectivity patterns

We observed no differences between ASD, OCD, and healthy control groups in any of the seed regions' connectivity patterns. However, the dimensional analysis across all participants showed a positive association between repetitive behaviour and connectivity strength between the left NAcc and a cluster in the right premotor cortex/middle frontal gyrus (MFG; see Figure 2). The correlation of the extracted average connectivity estimates with repetitive behaviour was $r_s=0.40$, $p<.001$ across the entire sample; and $r_s=0.47$, $p<.001$ in ASD and OCD together, without controls. Trends were present in the ASD ($r_s=0.41$; $p=.052$) and OCD ($r=0.39$; $p=.054$) groups when investigated separately. This suggests that the association was not driven by a dichotomy between patients and controls or by a specific diagnostic group. Lastly, there were no interactions between diagnosis and repetitive behaviour for the ASD and OCD groups; in other words, there was no evidence for distinct neural correlates of repetitive behaviour in ASD versus OCD.

Sensitivity analyses

There were no significant correlations between the left NAcc - right premotor cortex/MFG connectivity estimates and either IQ ($r=-0.08$; $p=.519$) or head motion (RMS-FD; $r_s=-0.07$; $p=.568$). Furthermore, the positive association between repetitive behaviour and left NAcc – right premotor connectivity remained significant after the removal of two outliers ($r_s=0.35$; $p=.002$). Scan-site, sex, and age were added as covariates in these analyses. The sensitivity analyses described in the supplement indicate that the correlation between repetitive behaviour and connectivity between the left NAcc and right premotor cortex was similar across sexes and scan-sites, and was also significant in those without concurrent comorbid disorders or medication use (also see Supplementary Figures 3-8).

Discussion

The aim of the present study was to investigate overlapping and diagnosis-specific abnormalities of resting state frontostriatal connectivity in children and adolescents with ASD and OCD. Additionally, we assessed whether the cross-disorder symptom dimension of compulsivity/repetitive behaviour was associated with shared connectivity patterns in frontostriatal pathways across both ASD and OCD. We did not detect differential connectivity of striatal seed regions specific to ASD or OCD diagnosis. However, the cross-disorder analysis showed that increased connectivity between the left NAcc and a cluster in the right premotor cortex/MFG was related to more severe symptoms of repetitive behaviour across the entire sample. This finding was partly in keeping with our hypotheses; we predicted increased connectivity of the NAcc, albeit with a different frontal region, the OFC. In contrast to our hypotheses, we did not find altered connectivity of the caudate or putamen in relation to repetitive behaviour.

The observed association between repetitive behaviour and increased NAcc – premotor/MFG connectivity is in line with the relatively well-established role for altered functioning of the NAcc in OCD. Numerous resting state studies in OCD have shown increased connectivity of the NAcc, mainly with the OFC (Harrison *et al.* 2009, 2013; Sakai *et al.* 2011; Jung *et al.* 2013; Abe *et al.* 2015); a finding which has also been reported in ASD (Delmonte *et al.* 2013; although see Padmanabhan *et al.* 2013). This finding might reflect an increased motivational drive towards performing certain repetitive behaviours. In addition, blunted activity of the NAcc during (monetary) reward anticipation was found in individuals with ASD (Dichter *et al.* 2012a, 2012b; Kohls *et al.* 2013) and OCD (Figeet *et al.* 2011, 2013), suggesting altered sensitivity to typical rewards. Of particular interest is the study by Figeet *et al.* (2013) where deep brain stimulation in OCD restored blunted NAcc activity and excessive resting state connectivity between NAcc and lateral frontal cortex, with the degree of normalization correlating with symptom improvement. This implies a causal role for NAcc – lateral prefrontal connectivity in compulsivity.

Our obtained cluster in the premotor cortex/MFG can be compared to reports of MFG function more broadly or of premotor cortex (within the MFG) function more specifically. Dysfunction of the MFG has been implicated in ASD before, for example, in the context of social cognition (Patriquin *et al.* 2016) and in R-fMRI studies (Paakki *et al.* 2010; Delmonte *et al.* 2013; Itahashi *et al.* 2015). Notably, increased right MFG functional connectivity with the caudate was found to be associated with repetitive behaviour (Delmonte *et al.* 2013), further supporting the notion that the interplay between right MFG and striatum is involved in repetitive behaviour in ASD. Some evidence also points to a role of the MFG in OCD (e.g. Del Casale *et al.* 2016; Lázaro *et al.* 2008;

Togao *et al.* 2010); for example, hypoactivation was seen during executive functioning (Del Casale *et al.* 2016). Less evidence, however, exists regarding altered function of the premotor cortex. In OCD, previous literature has mainly described evidence implicating other motor regions such as the (pre) supplementary motor area (de Wit *et al.* 2012; Russo *et al.* 2014; Zhou *et al.* 2017). In ASD, research has focused predominantly on social impairments, leaving the motor domain neglected. Deficits in motor regions are commonly discussed within the framework of action prediction and the mirror neuron system (e.g. von Hofsten & Rosander 2012). However, it appears that the premotor cortex plays an atypical role in the later stages of visuomotor learning in ASD (Müller *et al.* 2004). Moreover, the premotor cortex is a conceptually relevant area considering it is responsible for implementing learned action patterns (Leisman *et al.* 2016). The link of premotor functioning with compulsivity/repetitive behaviour has been made more explicitly for tics in Tourette syndrome (Polyanska *et al.* 2017) and for automatized motor responses towards drug-related cues in addiction (Yalachkov *et al.* 2010).

Our finding of increased NAcc – premotor connectivity further confirms a role for altered NAcc connectivity in OCD and ASD and expands upon previous literature by showing a common pattern in functional connectivity underlying the overlapping symptom domain of repetitive behaviour. With the RBS-R capturing both OCD-like compulsions such as checking and counting, and more ASD-like repetitive behaviour such as preoccupations with certain objects or interests, we believe that this alteration reflects a general pathway where these behaviours may intersect. A shared dysfunction in reward or motivational processing of the NAcc with a strong connection to the premotor cortex implementing learned action patterns could explain the frequent comorbidity and familial link of these behaviours (Meier *et al.* 2015) in patients with ASD or OCD. This provides

a new avenue for further research that could also be relevant for conceptually related disorders of compulsivity such as Tourette syndrome and addiction.

In the present study, we did not replicate previous findings on group differences related to OCD and ASD diagnosis in the limbic (e.g. Abe *et al.* 2015; Delmonte *et al.* 2013; Harrison *et al.* 2009, 2013; Jung *et al.* 2013; Sakai *et al.* 2011; Vaghi *et al.* 2017), cognitive (e.g. Delmonte *et al.* 2013; Hou *et al.* 2013), or sensorimotor (e.g. Bernstein *et al.* 2016; Harrison *et al.* 2009; Padmanabhan *et al.* 2013; Vaghi *et al.* 2017) frontostriatal circuits. An explanation for the inconsistency in case-control differences might be the heterogeneity of symptom representation within the disorders (Langen *et al.* 2011; Robbins *et al.* 2012). For example, ASD has two defining symptom domains along which patients can vary. With the dimensional approach, we are more sensitive to detect a specific relation with the symptom dimension of repetitive behaviour, but our findings may diverge from those that are more linked to, for example, the social deficits in ASD or anxiety in OCD. In addition, differences in age groups may explain discrepancies in results since frontostriatal circuits develop across a long period (Durstun & Casey 2006) and the neurobiological markers of a disorder may vary over time. Of the abovementioned studies, only one included children. Especially for OCD, the differences between child and adult findings may be large since late-onset OCD may have a different aetiology (Taylor 2011).

By studying children and adolescents, we focused on an important, but scarcely studied developmental window and avoided confound with late-onset OCD. However, due to difficulties in recruiting children with an OCD diagnosis, our sample is relatively small and also includes mild cases. This may have limited the power to detect effects. In light of the limited power, we chose

not to apply additional corrections for the number of seed regions used in the analyses. This is considered appropriate for studies with a small set of clear hypotheses, to avoid type 2 errors (Streiner & Norman 2011). However, the results should be interpreted with caution. An additional complication of the current study is that the RBS-R has been specifically designed for and validated in ASD (Lam & Aman 2007). Nevertheless, the RBS-R total scores in OCD correlated highly with the CY-BOCS scores, which provides some confidence in the extrapolation of this measure to OCD. Overall, this young field is still faced with the challenge of unifying classifications of repetitive behaviour and designing instruments for cross-disorder analysis. This is not trivial, because phenotypic similarity does not necessarily imply a shared aetiology and vice versa (Langen *et al.* 2011). However, an attempt has been made to design such an instrument (Guo *et al.* 2017), which holds promise for future applications in cross-disorder research of compulsivity.

To conclude, we found increased connectivity of the left NAcc with the right premotor cortex in relation to repetitive behaviour across children and adolescents with OCD, ASD, and healthy controls. Hereby, we demonstrate the fruitfulness of applying a cross-disorder approach to the symptom domain of compulsivity/repetitive behaviour, and reveal for the first time a shared neural correlate potentially reflecting altered reward or motivational processing of the NAcc with excessive connectivity to the premotor cortex implementing learned action patterns.

Acknowledgments

The TACTICS Consortium consists of Jan Buitelaar, Saskia de Ruiter, Jilly Naaijen, Sophie Akkermans, Maarten Mennes, Marcel Zwiers, Shahrzad Ilbegi, Leonie Hennissen, Jeffrey Glennon, Ilse van de Vondervoort, Katarzyna Kapusta, Natalia Bielczyk, Houshang Amiri, Martha Havenith, Barbara Franke, Geert Poelmans, Janita Bralten, Tom Heskes, Elena Sokolova, Perry

Groot from Radboud University Medical Center Nijmegen, the Netherlands; Steven Williams, David Lythgoe, Muriel Bruchhage, Iulia Dud from Kings College London, United Kingdom; Ralf Dittmann, Tobias Banaschewski, Daniel Brandeis, Konstantin Mechler, Ruth Berg, Isabella Wolf, Alexander Häge, Sarah Hohmann, Regina Boecker-Schlier, Matthias Ruf from Central Institute of Mental Health, Medical Faculty Mannheim/University of Heidelberg, Mannheim, Germany; Rick Dijkhuizen, Erwin Blezer, Kajo van der Marel, Pim Pullens, Wouter Mol, Annette van der Toorn, Willem Otte, Caroline van Heijningen, Sarah Durston, Vincent Mensen, Bob Oranje, René Mandl from University Medical Center Utrecht, Utrecht, the Netherlands; Daphna Joel from Tel Aviv University, Tel Aviv, Israel; John Cryan from University College Cork, Cork City, Ireland; Tracey Petryshen, David Pauls, Mai Saito from Massachusetts General Hospital, Boston, USA; Angelique Heckman from Genoway, Lyon, France; Sabine Bahn from University of Cambridge, Cambridge, United Kingdom; Ameli Schwalber from Concentris, München, Germany; and Philippe Auby from Lundbeck, Valby, Denmark. We gratefully acknowledge the contribution of all our participants and their families, and all researchers involved in data collection.

Financial support

This work was supported by the European Community's Seventh Framework Programme FP7/2007-2013 under grant number 278948 (TACTICS). This funding agency had no role in study design, data collection, interpretation or influence on writing.

Conflict of interest

J.K. Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Medice, Lundbeck, Roche and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies.

He has no other financial or material support, including expert testimony, patents, and royalties.
All other authors have no conflicts of interest to report.

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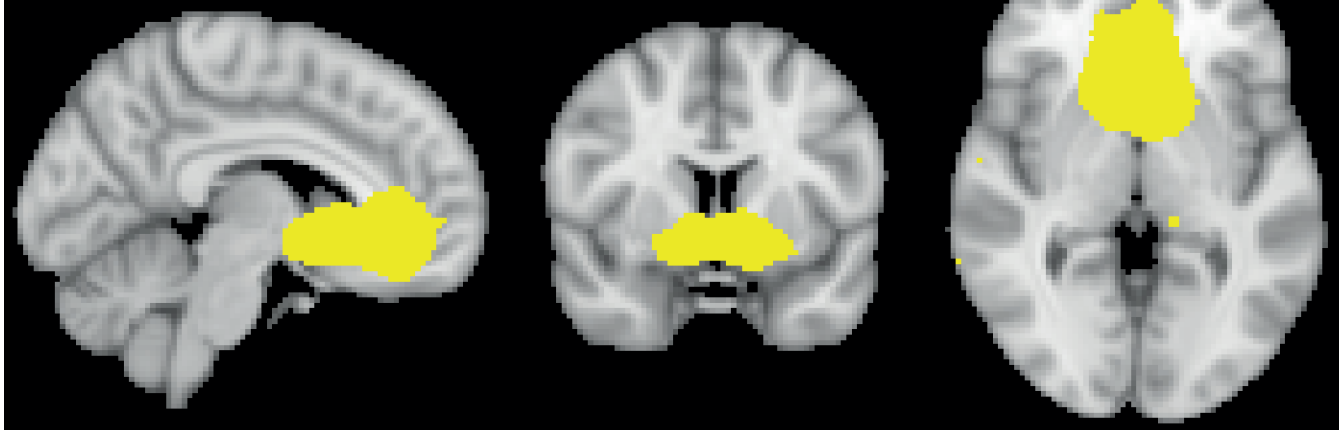
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Figure 1. Whole-brain functional connectivity maps for different striatal seeds.

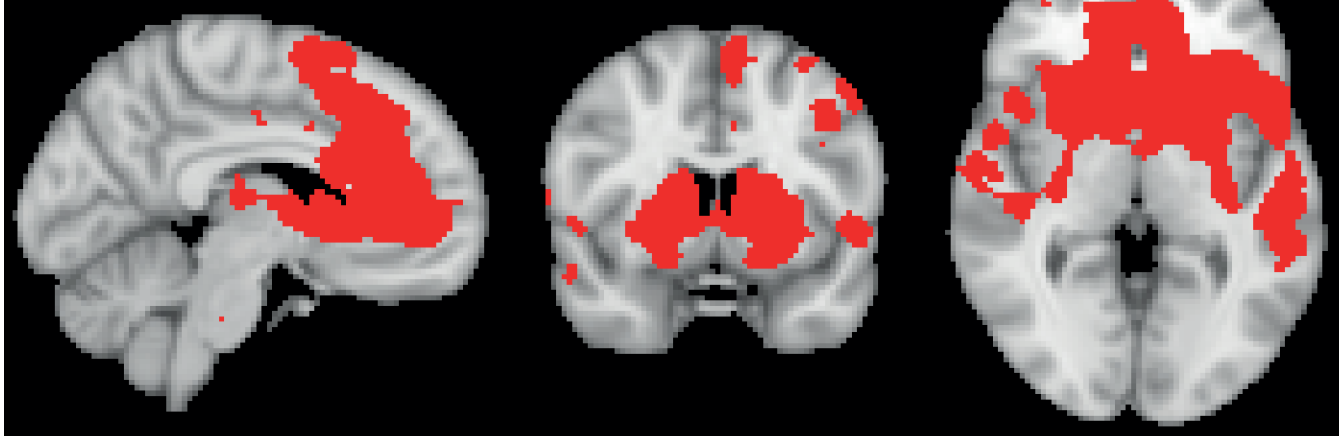
Whole-brain positive functional connectivity maps are shown for the left nucleus accumbens (NAcc), caudate nucleus, anterior (ant) putamen, and posterior (post) putamen in healthy controls (N=29). Connectivity maps are thresholded at $p < 0.05$, FWE-corrected and $t \geq 5$; all maps are displayed at X=-6, Y=6, Z=0 in MNI152-space.

Figure 2. Repetitive behaviour is positively associated with left nucleus accumbens – right

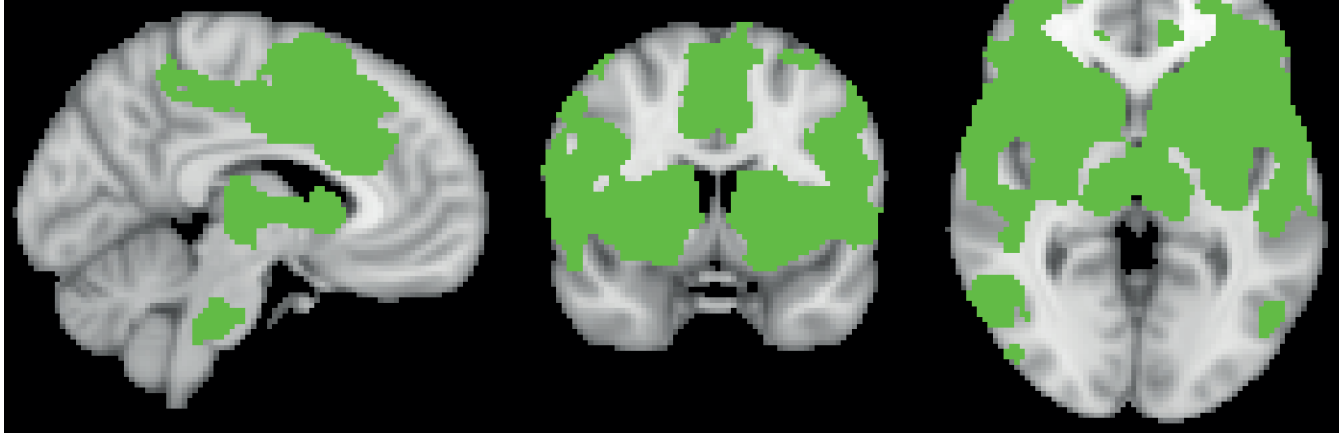
premotor connectivity. A) Significant positive association of repetitive behaviour with functional connectivity between the left nucleus accumbens seed (example from one participant in green) and the right premotor cortex/middle frontal gyrus (in red). Results are thresholded at $p < 0.05$, FWE-corrected. Coordinates are in MNI152-space. B) Association between repetitive behaviour (RBS-R total score) and extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex represented for the diagnostic groups separately. Linear associations (lines) are presented for the diagnostic groups separately (coloured) and across all participants (black).



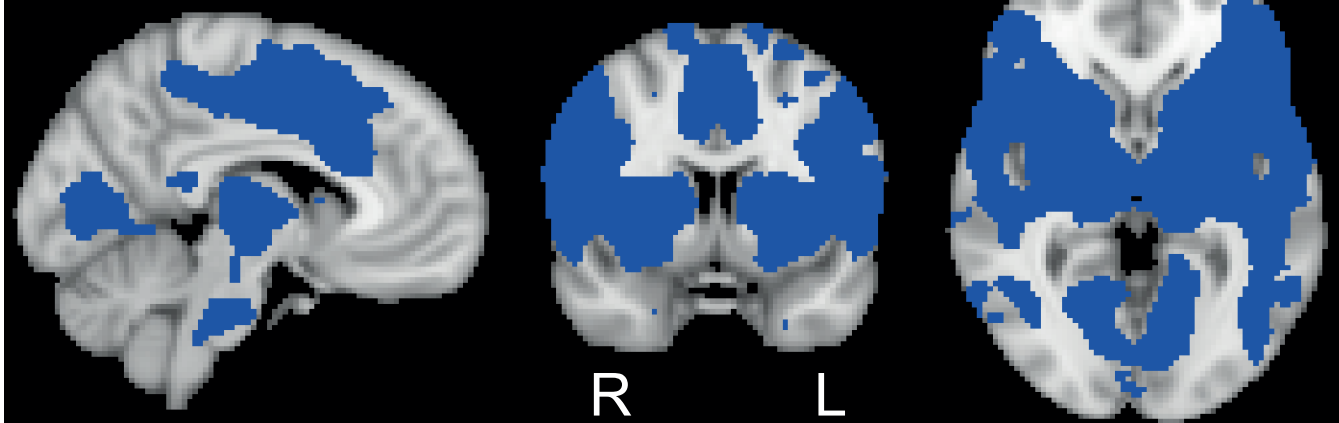
Caudate



Ant Putamen



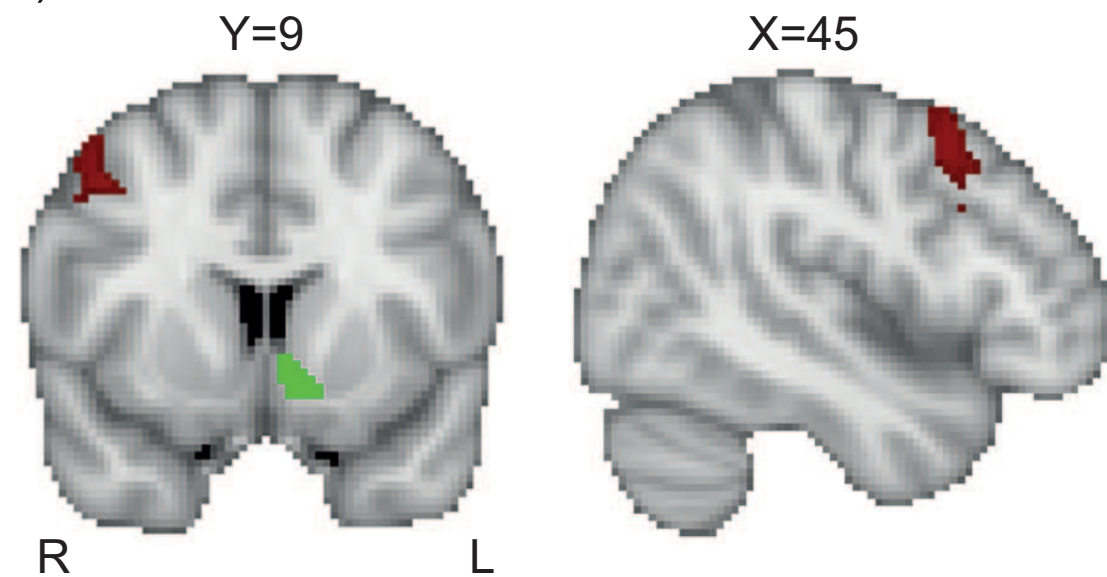
Post Putamen



R

L

A)



B)

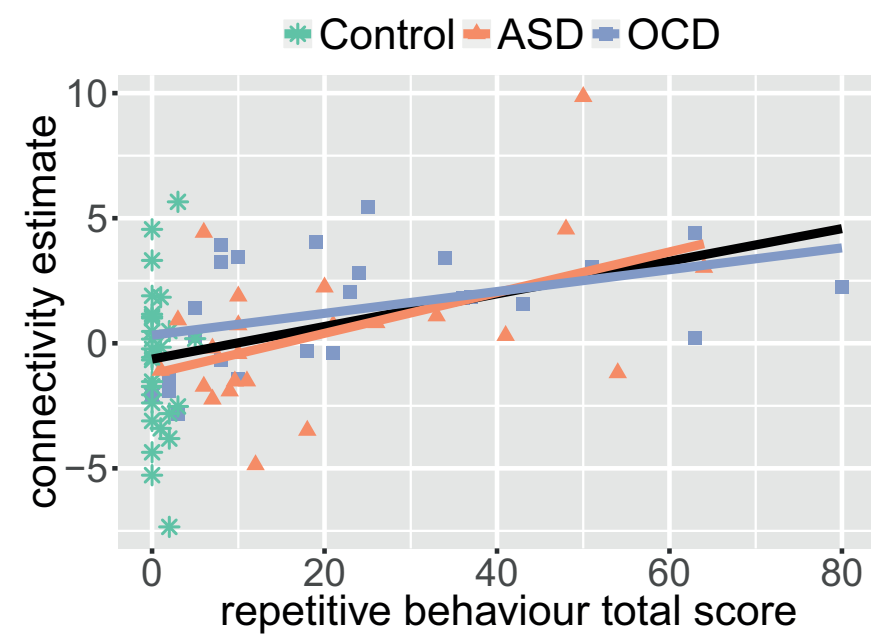


Table 1. Group characteristics

	Control	ASD	OCD	Test statistic	<i>p</i>-value
<i>n</i> (% males)¹	29 (66)	24 (54)	25 (64)	$\chi^2=0.81$.667
Nijmegen	16 (63)	11 (9)	16 (56)		
London	13 (69)	13 (92)	9 (78)		
Age in years² <i>M</i> (<i>SD</i>)	11.6 (2.0)	11.8 (2.2)	11.9 (2.3)	$F(2,75)=0.10$.905
IQ^{2,3} <i>M</i> (<i>SD</i>)	106.2 (13.2)	101.0 (15.9)	106.9 (17.3)	$F(2,72)=1.04$.358
Head motion^{2,4} <i>M</i> (<i>SD</i>)	0.14 (0.13)	0.15 (0.13)	0.16 (0.12)	$\chi^2=1.25$.534
RBS-R total score⁵ <i>M</i> (<i>SD</i>)	0.8 (1.3)	20.7 (18.4)	23.9 (22.0)	$t(46)=0.54$.590
CY-BOCS⁶ <i>M</i> (<i>SD</i>)					
Total score	-	-	21.3 (6.1)		
Compulsions	-	-	10.9 (2.9)		
Obsessions	-	-	10.1 (3.7)		
Current medication use, <i>n</i>					
SSRI	-	1	6		
Stimulant	-	0	2		
Benzodiazepine	-	0	2		
Atypical antipsychotic	-	1	4		
Classical antipsychotic	-	1	0		
Current comorbidity, <i>n</i>					
ADHD	-	4	5		
ODD	-	0	1		
GAD	-	0	2		
Depressive disorder	-	1	0		
Tic disorder	-	0	7		

¹A chi-square test was employed to test the difference in proportion of males between the groups.

²Differences between groups were tested by means of an analysis of variance (ANOVA) or, if parametric assumptions were not met, the non-parametric Kruskal-Wallis test. ³Estimated IQ was based on 4 Wechsler Intelligence Scale for Children–III subtests: block design, vocabulary, similarities, and picture completion. IQ scores were missing for three participants. ⁴Head motion is defined as the mean root mean square of the frame-wise displacement across functional scans (Jenkinson *et al.* 2002). ⁵RBS-R total scores can range

from 0-129. Data from one participant was missing. An independent-samples *t*-test was performed to test the difference between the ASD and OCD groups. ⁶CY-BOCS total scores can range from 0-40. For three participants a total score could not be computed due to the absence of obsessions. CY-BOCS total scores were significantly correlated (Spearman) with RBS-R total scores: $r_s=0.69$; $p<.001$. Abbreviations: ADHD – attention-deficit/hyperactivity disorder, ASD – autism spectrum disorder, CY-BOCS – Children’s Yale-Brown Obsessive Compulsive Scale, GAD – generalized anxiety disorder, OCD – obsessive-compulsive disorder, ODD – oppositional defiant disorder, RBS-R – Repetitive Behavior Scale-Revised, SSRI – selective serotonin reuptake inhibitor.

Supplementary information

Frontostriatal functional connectivity correlates with repetitive behaviour across autism spectrum disorder and obsessive-compulsive disorder

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Table S1. Scanning parameters per site

Sequence	Site	TR/TE/TI (ms)	Flip angle	Field of view (mm)	Matrix RL/AP /slices	Voxel-size (mm)	Parallel Imaging
T1*	Nijmegen <i>(Siemens Prisma)</i>	2300/2.98/900	9	256	212/256/176	1.0 × 1.0 × 1.2	2
	London <i>(GE MR750)</i>	7.31/3.02/400	11	270	256/256/196	1.1 × 1.1 × 1.2	1.75
R-fMRI#	Nijmegen <i>(Siemens Prisma)</i>	2300/12/-	80	240	240/240/33	3.8 × 3.8 × 3.8	2
	London <i>(GE MR750)</i>	2300/13/-	80	240	240/240/33	3.8 × 3.8 × 3.8	2

*TR as provided by the manufacturer. Siemens defines TR as the time between inversion recovery pulses per volume, whereas GE defines a TR as the time an excitation pulse is given.
#Multi-echo resting state fMRI: TE2 is 31 ms for London and 28.41 for Nijmegen. TE3 is 48 for London and 44.82 for Nijmegen.

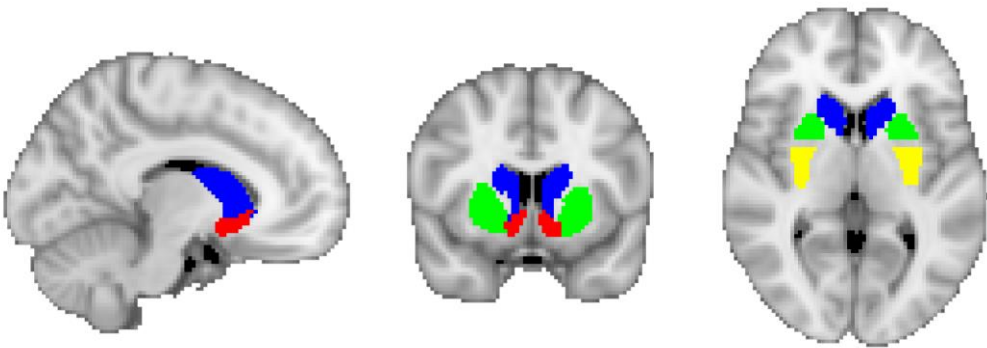


Figure S1. Seed regions. The seed regions displayed here are an example from one participant overlaid on an MNI152 template brain. Legend: blue – caudate nucleus, red – nucleus accumbens, green – anterior putamen, yellow – posterior putamen. Note that left and right volumes were analysed separately.

Sensitivity analyses: influence of scan-site, sex, and age

In all instances full Spearman correlations are reported. As can be seen in Figure S2, age was not related to connectivity between the left nucleus accumbens and right premotor cortex ($r_s=0.10$; $p=.393$). Figures S3 to S6 demonstrate that the association between repetitive behaviour and the connectivity estimates was significant in both males ($n=47$; $r_s=0.37$; $p=.010$) and females ($n=30$; $r_s=0.47$; $p=.009$); and either trend level in London ($n=34$; $r_s=0.30$; $p=.085$) or significant in Nijmegen ($n=43$; $r_s=0.53$; $p<.001$). These results suggest that the effect was not specific to males or females, or scan-site.

Sensitivity analyses: influence of medication use and comorbidity

The association (uncorrected for age, sex, scan-site) between repetitive behaviour and the connectivity estimates was significant in participants who currently did not use medication ($n=62$; $r_s=0.35$; $p=.006$) and in participants without comorbid disorders ($n=63$; $r_s=0.36$; $p=.003$). These results suggest that the effect was not driven by participants with concurrent medication use or comorbid disorders (also see Figure S7 and S8).

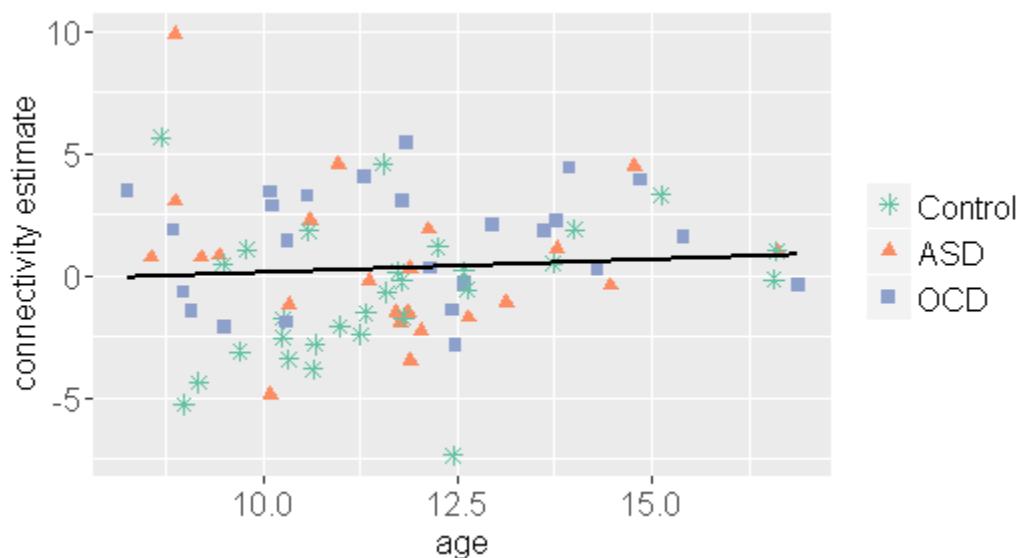


Figure S2. No association was present between age and connectivity. Line represents linear association across all groups between age in years and extracted estimates of connectivity between left nucleus accumbens and right premotor cortex.

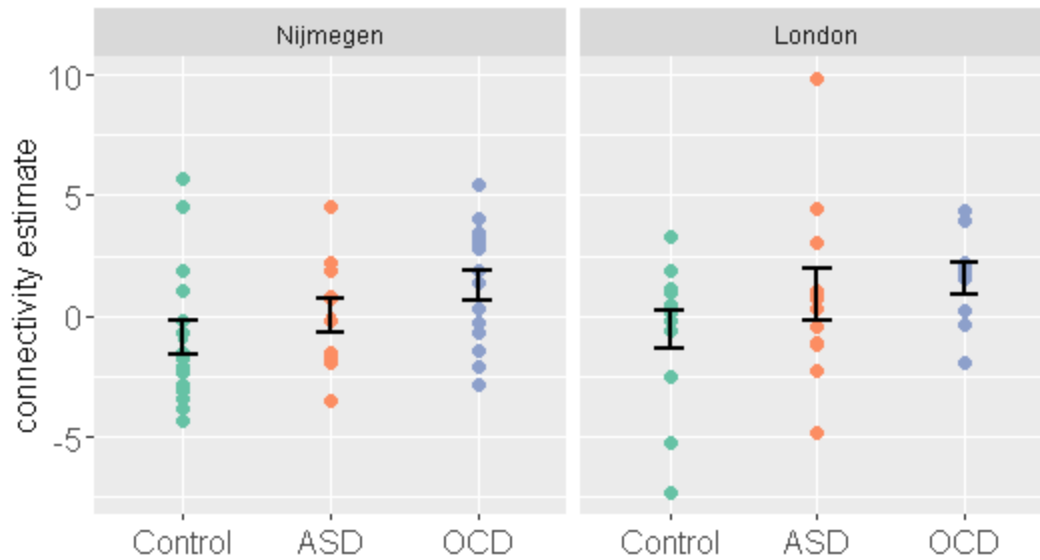


Figure S3. Extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex represented for the diagnostic groups and scan-sites separately. Errorbars denote means \pm SE.

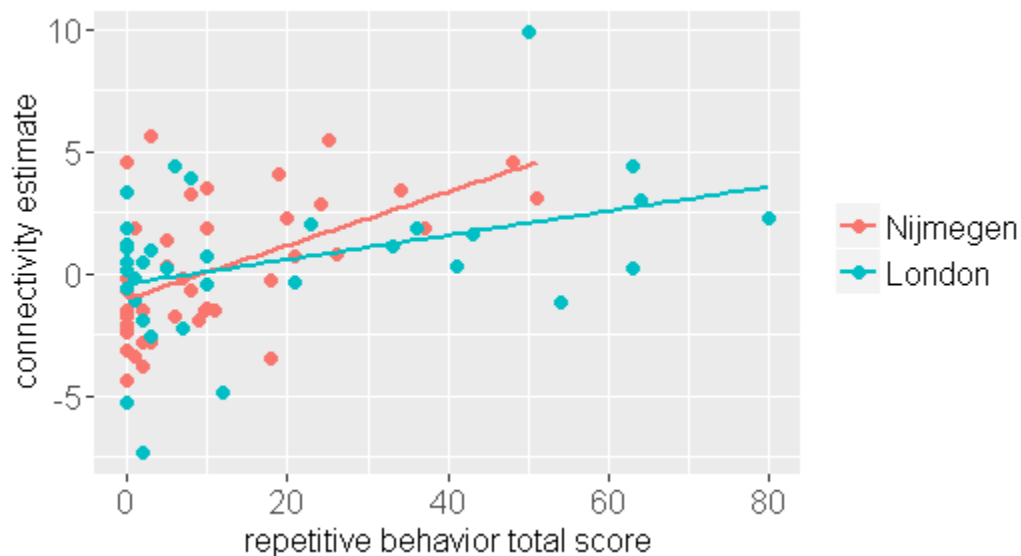


Figure S4. A positive association between repetitive behaviour and connectivity was present in both Nijmegen and London. Lines represents linear associations between repetitive behavior (RBS-R total score) and extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex, represented for Nijmegen and London separately.

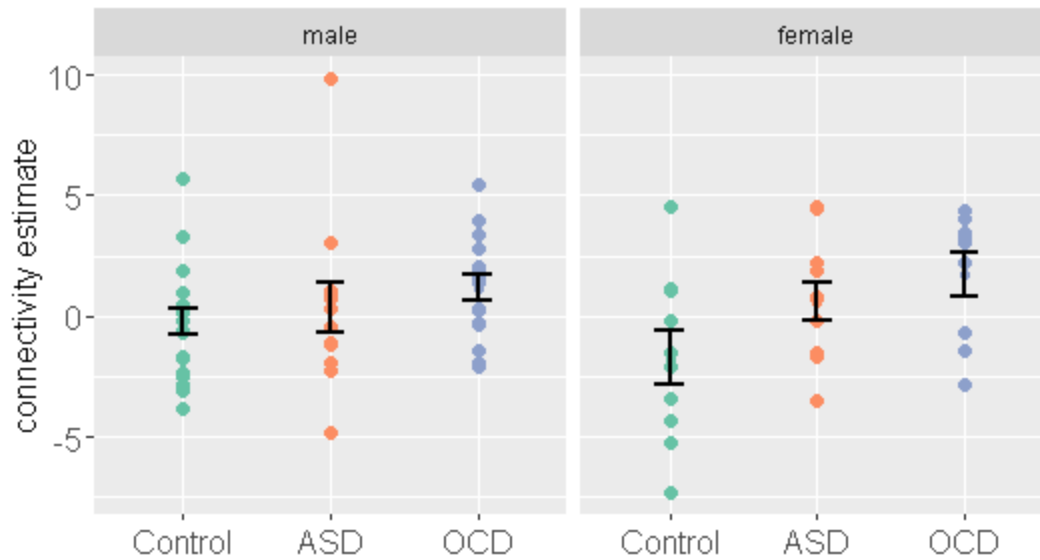


Figure S5. Extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex represented for the diagnostic groups and males and females separately. Errorbars denote means \pm SE.

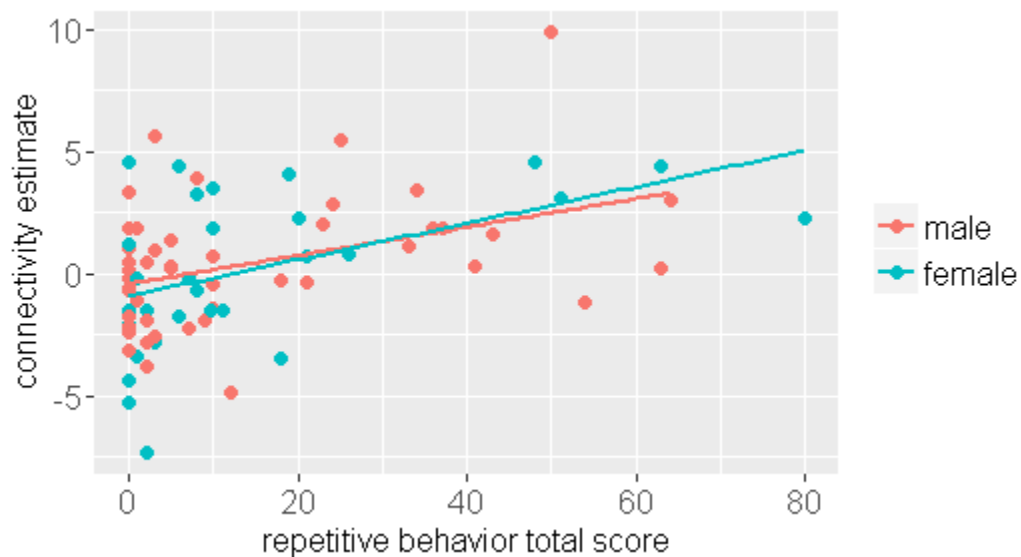


Figure S6. A positive association between repetitive behaviour and connectivity was present in both males and females. Lines represents linear associations between repetitive behaviour (RBS-R total score) and extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex, represented for males and females separately.

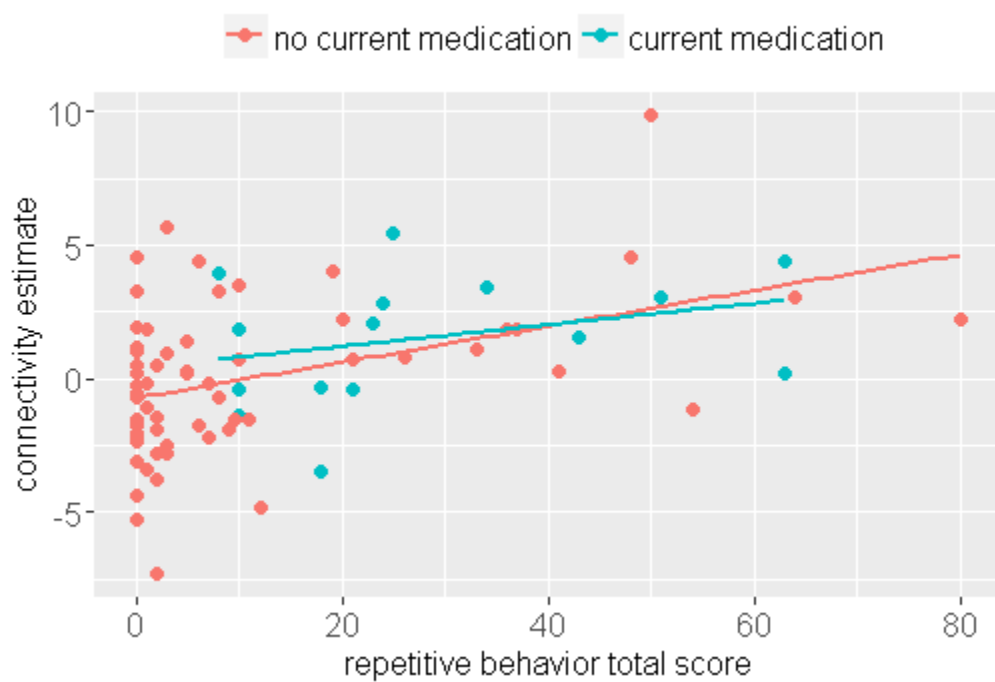


Figure S7. A positive association between repetitive behaviour and connectivity was also present in those without current medication use. Lines represents linear associations between repetitive behaviour (RBS-R total score) and extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex, represented for those with and without current medication use separately.

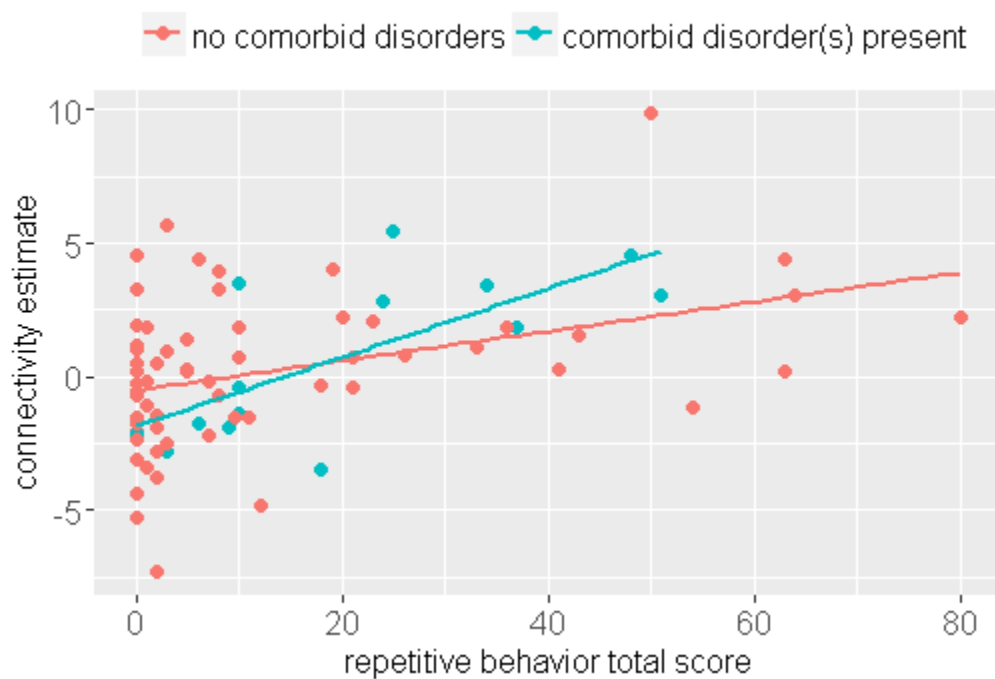


Figure S8. A positive association between repetitive behaviour and connectivity was also present in those without current comorbid disorders. Lines represents linear associations between repetitive behaviour (RBS-R total score) and extracted estimates of connectivity between the left nucleus accumbens and right premotor cortex, represented for those with and without current comorbid disorders separately.